AN OPEN-LABEL, PHASE 1, RANDOMIZED STUDY TO EVALUATE THE BIOAVAILABILITY OF APIXABAN (BMS-562247) 0.1-mg SPRINKLE CAPSULES RELATIVE TO REFERENCE 0.5-mg TABLETS IN HEALTHY PARTICIPANTS

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STATISTICAL ANALYSIS PLAN FOR
RELATIVE BIOAVAILABILITY OF APIXABAN (BMS-562247) 0.1-MG SPRINKLE CAPSULES COMPARED WITH 0.5-MG TABLETS IN HEALTHY PARTICIPANTS

VERSION # FINAL 1.0

Revision History

Revision	Date	Revised By	Changes Made -- Reasons for the Change
Final 0.1	04-Jun-2018	[redacted]	Initial draft based on Original Protocol dated 31-Mar-2018 and administrative letter dated 12-Apr-2018

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[redacted]

Schedule of Analyses:

Final analysis will be performed following database lock according to agreed-upon reporting milestone(s), typically after all participants have completed the study.

2 STUDY DESCRIPTION

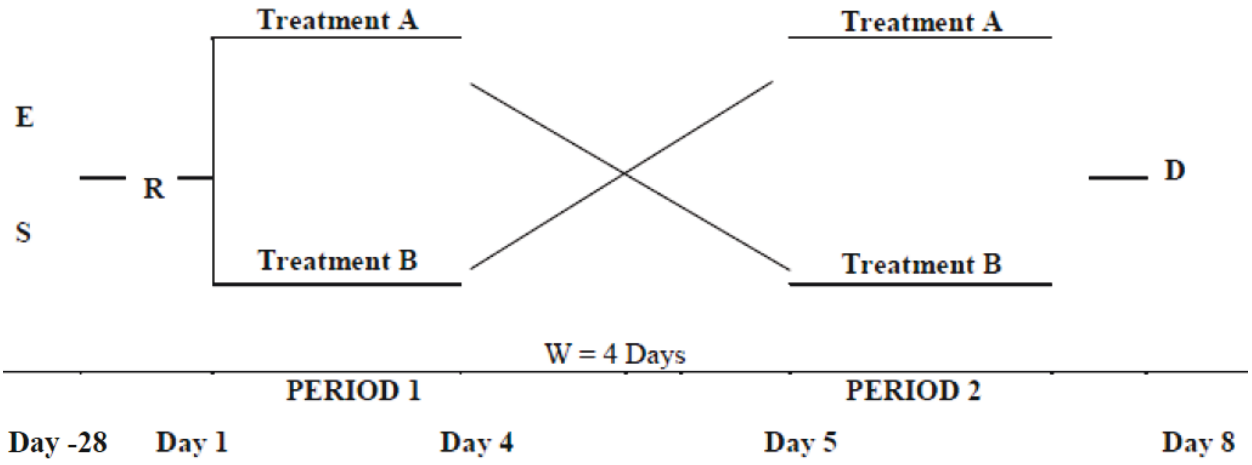
2.1 Study Design

This is a Phase 1, open-label, randomized, 2-period, 2-treatment crossover study in healthy participants. Healthy male or female participants as determined by medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests will be

eligible to participate in the study. Participants will undergo screening evaluations to determine eligibility within 28 days prior to study treatment administration. On Day -1, participants will enter the clinical facility and be confined for the duration of the study, until discharge on Day 8. Prior to dosing on Day 1 of Period 1, participants will be randomly assigned to 1 of 2 treatment sequences (AB or BA, where Treatment A is 5 × 0.5-mg apixaban tablets and Treatment B is 25 × 0.1-mg apixaban sprinkle capsules) in a 1:1 ratio. Participants will receive a single oral dose of apixaban on Days 1 and 5. There will be a 4-day washout period between doses. Treatments A and B will be prepared in the pharmacy.

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1 Study Design Schematic



D = Study Discharge; E = Enrollment; R = Randomization; S = Screening; Treatment A = 5 × 0.5-mg apixaban tablets; Treatment B = 25 × 0.1-mg apixaban sprinkle capsules; W = Washout

Physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout the study. Participants will be closely monitored for adverse events (AEs) throughout the study. Blood samples will be collected for up to 72 hours after study drug administration for pharmacokinetic (PK) analysis. Approximately 240 mL of blood will be drawn from each participant during the study.

Participants will complete a palatability assessment immediately (within 5 minutes) after administration of the apixaban 0.5-mg tablet and 0.1-mg sprinkle capsule dosages, on both Day 1 and Day 5.

2.2 Treatment Assignment

Eligible participants will be randomized in a 1:1 ratio to 1 of 2 treatment sequences according to a computer-generated randomization scheme prepared by PPD.

Study treatment will be administered on Days 1 and 5.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). Those enrolled participants meeting

inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment. The Sponsor (or designee) may replace participants for other reasons. If a participant is replaced after dosing then the replacement participant will be assigned the original participant's number plus 100. The replacement participant will receive the same treatments as the participant being replaced but a new randomization number will be assigned to him or her. For example, Participant 4 would be replaced by Participant 104.

2.3 Blinding and Unblinding

This is an open-label study.

2.4 Protocol Amendments

This statistical analysis plan (SAP) reflects the administrative letter, dated 12 April 2018.

3 OBJECTIVES

3.1 Primary

The primary objective for this study is to assess the bioavailability of apixaban 0.1-mg sprinkle capsules relative to apixaban 0.5-mg tablets, both administered orally in healthy participants.

3.2 Secondary

The secondary objectives for this study are:

- To assess the safety and tolerability of apixaban
- To assess the PK of apixaban 0.1-mg sprinkle capsules
- To assess the PK of apixaban 0.5-mg tablets

[redacted]

4 ENDPOINTS

4.1 Efficacy Endpoints

There are no planned efficacy endpoints.

4.2 Safety Endpoints

Safety endpoints include incidence of nonserious AEs, serious AEs (SAEs), AEs leading to discontinuation or death, as well as marked abnormalities in clinical laboratory tests, vital sign measurements, 12-lead ECGs, and physical examinations.

4.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters of apixaban will be derived from the respective plasma concentration versus time data. Individual PK parameter values will be derived by non-compartmental methods by a validated PK analysis program using actual times.

The primary PK endpoints are:

- Cmax, AUC(INF), and AUC(0-T) of apixaban.

The secondary PK endpoints are:

- Tmax, T-HALF, and Frel of apixaban.

Specific PK parameters are shown in Table 4.3-1.

Table 4.3-1: Pharmacokinetic Parameters, Naming Conventions and Definitions

Parameter	Definition
Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
T-HALF	Terminal plasma half-life
Frel	Relative bioavailability

[redacted]

5 SAMPLE SIZE AND POWER

The similarity of the bioavailability will be concluded if the 90% confidence interval (CI) for the ratio of geometric means of apixaban 0.1-mg sprinkle capsules relative to apixaban 0.5-mg tablets are wholly contained within 80% and 125% for Cmax and AUC. The following table shows the power provided with data from 28 PK evaluable participants based on different assumptions of difference between the bioavailability of apixaban 0.1-mg sprinkle capsules and apixaban 0.5-mg tablets.

True Geometric Mean Ratio	Power of Cmax	Power of AUC(0-T)	Power of AUC(INF)	Overall Power
1	99%	99%	99%	97%
1.02	99%	99%	99%	97%
1.04	98%	99%	99%	96%
1.06	96%	99%	99%	94%
1.08	91%	99%	99%	89%
1.1	83%	99%	99%	81%

As an example, if there is a 10% difference between the bioavailability of apixaban 0.1-mg sprinkle capsules and apixaban 0.5-mg tablets, then data from 28 PK evaluable participants will provide approximately 83%, 99%, and 99% power to conclude similar bioavailability for Cmax, AUC(INF), and AUC(0-T), respectively. The overall power for this hypothesis is approximately 81%.

These calculations use the approach described by Diletti et al.[5] and assume Cmax and AUC are log normally distributed with intra-subject coefficient of variation (%CV) of 18% for Cmax and 12% for AUC, as estimated from apixaban Study CV185111[4] and Study CV185292[6]. To allow for possible dropouts, a total of 30 participants are planned to be randomized to obtain at least 28 PK-evaluable participants.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- The pre-treatment period will be from the time the Informed Consent Form (ICF) is signed until the time just prior to dosing on Day 1 for all participants. The pre-treatment period should be no longer than 28 days and will include all screening, enrollment, Day -1, randomization, and Day 1 predose procedures.
- Period 1 will be from the time of dosing on Day 1 until the time prior to dosing in the next period on Day 5, or until study discharge due to premature discontinuation if the participant is not dosed on Day 5.
- Period 2 will be from the time of dosing on Day 5 until the participant is discharged on Day 8, or until the day of study discharge due to premature discontinuation after dosing on Day 5.
- If a participant is not discharged on Day 8, any data collected after Day 8 will be assigned to the post-treatment period.
- Periods 1 and 2 will be considered on-therapy for the purpose of safety analyses.

The definition of each study period is included in Table 6.1-1.

Table 6.1-1 Definition of Study Period

PERIOD SEQUENCE	PERIOD NAME	DATE TO BE USED	DEFINITION
1	PRE-TREATMENT	- CONSENT DATE - DOSE DATETIME ON DAY 1	Starting with consent date and ending by (<) dose date and time on Day 1
2	PERIOD 1	- DOSE DATETIME ON DAY 1 - DOSE DATETIME ON DAY 5	Starting with dose date and time on Day 1 and ending by (<) dose date and time on Day 5
3	PERIOD 2	- DOSE DATETIME ON DAY 5 - DISCHARGE DATE	Starting with dose date and time on Day 5 and ending by (≤) discharge date
4	POST-TREATMENT	- DISCHARGE DATE	Starting with discharge date + 1

6.2 Treatment Regimens

The following treatments will be administered in this study with a 1:1 ratio in sequences of AB and BA.

- Treatment A = 5 × 0.5-mg apixaban tablets
- Treatment B = 25 × 0.1-mg apixaban sprinkle capsules

6.3 Populations for Analyses

- Enrolled Population, defined as all participants who signed the ICF.
- Randomized Population, defined as all participants who are randomized to a sequence of treatments.
- Treated Population, defined as all participants who received at least 1 dose of study treatment.
- Pharmacokinetic Population, defined as all participants who received at least 1 dose of study treatment and had any available concentration-time data. Pharmacokinetic listings and PK parameter calculations will be based on this population.
- Evaluable PK Population is a subset of the Pharmacokinetic population. The Evaluable PK population includes all participants who had adequate PK profiles for accurate estimation of PK parameters and had no protocol deviations considered to affect the PK assessments.

All available derived PK parameter values will be included in the PK data set and reported, but only participants with evaluable PK data will be included in the summary statistics and statistical analysis.

7 STATISTICAL ANALYSES

SAS® version 9.3 or higher will be used for statistical analyses, tabulations and graphical presentations.

7.1 General Methods

All data recorded on case report forms (CRFs) will be listed by participant. Descriptive summaries will be presented for continuous variables using number of participants (N), mean, standard deviation (SD), median, minimum and maximum. Geometric mean and %CV will also be presented for sample plasma PK parameters. Descriptive summaries for categorical variables will utilize counts and percentages.

Where appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first dose of study treatment.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, version to be delineated in the clinical study report (CSR).

7.2 Study Conduct

Deviations from the study protocol, protocol amendments, and administrative changes will be documented. No potential protocol deviations are defined as being relevant in this healthy volunteer study; listing of relevant protocol deviations will not be provided.

7.3 Study Population

7.3.1 Participant Disposition

Participant disposition will be listed. Summary tables reflecting the number of participants who are enrolled, who are randomized, who are not randomized, and reasons for not being randomized will be presented as overall for the enrolled population.

The number of participants who complete the study, who do not complete the study, and reasons for not completing the study, will be summarized for the treated population, as overall and by treatment sequence.

7.3.2 Demographic Characteristics

Demographic characteristics such as gender, age, race, and ethnicity will be listed for the treated population. Demographic characteristics will also be summarized for the treated population, as overall and by treatment sequence.

7.3.3 Physical Measurements

Physical measurements such as body weight, height, and body mass index (BMI) will be listed for the treated population. Measurements will also be summarized by nominal visit for the treated population, as overall and by treatment sequence.

7.3.4 Medical History and Previous Medications

Medical history and previous medications taken prior to dosing will be listed for the treated population.

7.4 Extent of Exposure

No analysis regarding extent of exposure is planned. Randomization schedule will be listed for the randomized population. Study drug administration and batch numbers will be listed for the treated population. Any non-study medications taken by participants, any non-study medical treatment procedures conducted, and any non-study diagnostic procedures utilized will also be listed for the treated population.

7.5 Efficacy

There are no efficacy assessments in the study.

7.6 Safety

Analysis of all safety data will follow the BMS guideline of analysis of safety data. The evaluation of safety is based on clinical AEs, vital signs, ECG results, clinical laboratory results, and abnormal physical examinations reported during the study.

Unless otherwise specified, all safety presentations will utilize the treated population as described in Section 6.3.

All data collected from the sampling outside the scheduled visits will only be included in the listing and will be excluded from the summary tables.

7.6.1 Deaths

All deaths reported after a participant is enrolled (ie, has signed the ICF) will be listed for the enrolled population.

7.6.2 Serious Adverse Events

All reported SAEs will be listed for the enrolled population.

7.6.3 Adverse Events

Adverse events that occur on or after the first dose of study treatment will be tabulated. Events will be assigned to the last study treatment administered at the time of onset. Nonserious AEs occurring for up to 3 days after the termination of study treatment and SAEs occurring for up to 30 days after the termination of study treatment will be included in summary statistics. The proportion of participants having an AE will be calculated as the number of participants having the event in the specific treatment interval, divided by the total number of participants receiving study treatment during that treatment interval.

All AE listings will indicate the unique participant identifier, age, gender, current treatment, the date of onset, the date of resolution, day of onset relative to the start of treatment, action taken, investigator's assessment of severity and relationship to study drug. Additional listings will be provided for AEs leading to discontinuation and AEs without recorded resolution.

All AEs will be summarized by system organ class (SOC), preferred term (PT), treatment, and total for the treated population. Summaries of AEs will include AEs, AEs by intensity, and AEs related to study drug.

Adverse Event Counting Rules:

Where a participant has the same AE, based on PT, reported multiple times in a single analysis period, the participant will only be counted once at the PT level in AE frequency tables.

Where a participant has multiple AEs within the same SOC in a single analysis period, the participant will only be counted once at the SOC level in AE frequency tables.

When a participant has the same AE, based on PT, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study drug
- Intensity of event
- Onset date and time

When reporting AEs by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period, independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

Participants will only be counted once in the 'Total' at their maximum intensity, regardless of SOC or PT.

7.6.4 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests will be listed by participant for the treated population.

Laboratory evaluations will be reported both in conventional units and in International System of Units.

Laboratory results will be classified as markedly abnormal based on sponsor defined criteria. Laboratory results for participants with any marked laboratory abnormality (scheduled and unscheduled) will be listed for the treated population. This listing will include all observations for the specific laboratory test and participant, not only the marked laboratory abnormality measurements. The frequency of participants with any on-treatment marked laboratory abnormality, based on pre-specified criteria, will be presented for the treated population by treatment and total.

7.6.5 Electrocardiograms

All recorded ECGs will be listed for the treated population.

If QT interval corrected for heart rate using Fridericia's formula (QTcF) is not available in the database, QTcF will be calculated using the reported uncorrected QT Interval and heart rate, and the following formula:

$$QTcF = \frac{QT}{(60/HEART\ RATE)^{1/3}}$$

Participants with ECG intervals outside of a pre-specified range and investigator identified ECG abnormalities will also be listed for the treated population.

The following criteria will be used to determine ECG results that are outside of a pre-specified range:

PR (msec):	Value > 200
QRS (msec):	Value > 120
QT (msec):	Value > 500 or change from baseline > 30
QTcF (msec):	Value > 450 or change from baseline > 30

7.6.6 Vital Signs

Vital signs parameters (systolic blood pressure [BP], diastolic BP, heart rate, respiratory rate, and body temperature) will be listed for the treated population.

Participants with vital signs outside of a pre-specified range will also be listed for the treated population.

The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline are based on matched postural positions and are calculated as parameter value - baseline parameter value:

Heart Rate (bpm)	Value > 100 and change from baseline > 30, or Value < 55 and change from baseline < -15
Systolic BP (mmHg)	Value > 140 and change from baseline > 20, or Value < 90 and change from baseline < -20
Diastolic BP (mmHg)	Value > 90 and change from baseline > 10, or Value < 55 and change from baseline < -10
Respiration (breaths/min)	Value > 16 or change from baseline > 10
Temperature (°C)	Value > 38.3°C or change from baseline > 1.6°C

7.6.7 Physical Examination Findings

All physical examination abnormal findings will be listed per participant and visit for the treated population.

7.7 Pharmacokinetics

The PK population will be used for all PK listings. The Evaluable PK population will be used for summary statistics and statistical analyses. Analysis will include all valid analyte data for apixaban.

Participant plasma concentration-time profiles will be listed and summarized by treatment and nominal collection time for apixaban. Plots of individual plasma concentration profiles over time will be provided. Overlays of individual plasma concentration profiles over time will be provided by treatment. Plots of mean (+SD) plasma concentration profiles versus time will be presented for apixaban, and all treatments will be superimposed on the same plot.

All individual PK parameters will be listed for apixaban including any exclusions and reasons for exclusion. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and %CV will be presented for Cmax, AUC(0-T), AUC(INF), and Frel. Medians and ranges will be presented for Tmax. Means and SDs will be presented for other PK parameters (ie, T-HALF). Decimal place specifications for summary statistics are described in Section 7.9.

A linear mixed effect model with treatment and period as fixed effects and participant as repeated measures will be fitted to the log-transformed PK parameters (Cmax, AUC[0-T], and AUC[INF]) for use in estimation of effects and construction of CIs. Kenward-Rogers degrees of freedom will be specified in the model. Initial estimation of the variance/covariance will be based on an unstructured (UN) R matrix assuming no common variances or covariances; however, this UN matrix will be assessed and the more parsimonious compound symmetry (CS) R matrix will be imposed if assumptions of common variances and covariances are reasonable and can be supported by the data. Point estimates and 90% CIs will be exponentiated and results will be reported on the original scale.

Specific details with appropriate SAS code are provided below. Apixaban as 0.1-mg sprinkle capsules (Treatment B) is the test treatment and apixaban as 0.5-mg tablets (Treatment A) is the reference treatment in the analysis.

```
PROC MIXED DATA=PKDATA;
        BY [log transformed PK parameter such as Cmax, AUC(INF), AUC(0-T)];
        CLASS TREATMENT PERIOD USUBJID;
        MODEL LOG_PK = PERIOD TREATMENT / SOLUTION DDFM=KR;
        REPEATED TREATMENT / SUBJECT = USUBJID TYPE = UN R;
        LSMEANS TREATMENT / CL ALPHA=0.1;
        ESTIMATE 'B vs. A' TREATMENT -1 1 / E CL ALPHA=0.1;
RUN; QUIT;
```

Plots of individual treatment ratios of PK parameters (Cmax, AUC[INF], and AUC[0-T]) combined with geometric least square mean ratios (GMRs) and corresponding 90% CIs from the statistical analysis model, will also be provided. In addition, the GMRs and corresponding 90% CIs for AUC(0-T), AUC(INF), and Cmax for apixaban will be summarized in forest plots for overall assessment of the relative bioavailability of the test treatment (sprinkle capsules) compared to the reference treatment (tablets).

[redacted]

7.9 Conventions

EmBARC (Enhanced Biometric Analysis & Reporting Capability) standard time windowing, imputation rules, and counting rules will be applied.

7.9.1 Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the same precision as the data collected, 1 more decimal place for the mean, median, and SD, and 2 more decimal places for the standard error (SE). The GMR and the lower and upper limits of CI will be displayed to 3 decimal places.

For percent change from baseline data, minimum and maximum will be reported with 0 decimal places; mean, median, and SD will be reported with 1 decimal place; and SE will be reported with 2 decimal places.

The incidence rate will be rounded to 1 decimal place. If the incidence rate is less than 0.1%, then "<0.1" will be displayed.

Three decimal places for ratios will be used for data presentation.

7.9.2 Pharmacokinetic Summaries

In-text Tables

For in-text PK tables, %CV will be reported as integers. For other statistics except for SDs, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to 1 decimal place, and values of 1 - <10 will be displayed to 2 decimal places. Values less than 1 will be displayed to 3 decimal places. Ratios will also be displayed to 3 decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations[7]

For the summaries of plasma concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, predose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

All available plasma concentration-time data and derived PK parameter values will be included in the PK data set and listed accordingly.

Treatment of Outliers

If the predose concentration for a profile is greater than 5% of Cmax, then the PK parameters for that profile will be excluded from summaries and statistical analysis. Other individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis following

a review of available documentation (eg, bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire plasma concentration-time profiles for a participant may be excluded following review of available documentation (eg, bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Pharmacokinetic Exclusions

Pharmacokinetic Analysis, Reporting, and Exclusion criteria should follow the BMS PK Harmonization document Version 2.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 6.2 of the BMS PK Harmonization document.

Exclusion of one or more parameters or the entire dataset may be considered due to incomplete profile such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, participants may be excluded from the analysis if they missed doses, had diarrhea, or vomited at or before a time equal to twice the median Tmax for immediate-release products, or vomited at any time during sampling after the administration of modified-release formulations.

8 CONTENT OF REPORTS

Statistical components for the CSR will be based on the content of this SAP. Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific Data Presentation Plan (DPP).

9 List of Abbreviations

Table 9-1: List of Abbreviations

AE	adverse event
AUC	area under the concentration-time curve
AUC(0-T)	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	area under the plasma concentration-time curve from time zero extrapolated to infinite time
BMS	Bristol-Myers Squibb
BP	blood pressure
CI	confidence interval
Cmax	maximum observed concentration
CSR	clinical study report
%CV	coefficient of variation
FXa	Factor Xa
ECG	electrocardiogram
Frel	relative bioavailability
GMR	geometric mean ratio
ICF	informed consent form
LLOQ	lower limit of quantification
N	number of participants
PT	preferred term
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
T-HALF	terminal half life
Tmax	time of maximum observed plasma concentration
UN	unstructured

[redacted]

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